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ARTICLE

# Linkage and Associated Studies of Schizophrenia

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Genetic epidemiology has provided consistent evidence over many years that schizophrenia has a genetic component, and that this genetic component is complex, polygenic, and involves epistatic interaction between loci. Molecular genetics studies have, however, so far failed to identify any DNA variant that can be demonstrated to contribute to either liability to schizophrenia or to any identifiable part of the underlying pathology. Replication studies of positive findings have been difficult to interpret for a variety of reasons. First, few have reproduced the initial findings, which may be due either to random variation between two samples in the genetic inputs involved, or to a lack of power to replicate an effect at a given alpha level. Where positive data have been found in replication studies, the positioning of the locus has been unreliable, leading no closer to positional cloning of genes involved. However, an assessment of all the linkage studies performed over the past ten years does suggest a number of regions where positive results are found numerous times. These include regions on chromosomes 1, 2, 4, 5, 6, 7, 8, 9, 10, 13, 15, 18, 22 and the X. All of these data are critically reviewed and their locations compared. Reasons for the difficulty in obtaining consistent results and possible strategies for overcoming them are discussed. Am. J. Med. Genet. (Semin. Med. Genet.) 97:23–44, 2000. © **2000 Wiley-Liss, Inc.**

**KEY WORDS:** linkage; schizophrenia; genetics; complex trait

## INTRODUCTION

### Why Are We Looking for Genes Contributing to Schizophrenia?

A large body of data collected from families, twins and adoptees over many years has consistently supported the involvement of a major, complex genetic component in liability to schizophrenia and schizophrenia spectrum disorders.

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### Family Studies: Does Risk Aggregate in Relatives?

The combined results of many European studies published between 1921 and 1987 [Gottesman, 1991] are shown in Figure 1. The lifetime morbid risk (MR) in the general population is about 1%, but approximately 10 times that in the siblings or offspring of schizophrenics. Risk in parents is lower, possibly because having schizophrenia reduces fertility, and such parents are thus 'selected for health' [McGuffin et al., 1995] on the basis of having offspring. Smaller but consistent increases in MR are seen in second degree and third degree relatives. Risk also increases as more relatives are affected, for example from 9% if a just a sibling is ill to 17% if a sibling and one parent are affected. Risk is highest for monozygotic (MZ) twins (48%) and offspring of two schizophrenic parents (46%).

Criticisms of the methodology of early family studies included lack of proper controls, non-systematic methods of sampling, lack of standardized diagnostic criteria and failure to diagnose family members blind to the status of the index case (or proband). Data from 7 studies designed to answer these criticisms, when pooled and reanalyzed, however, yielded totals of 15 cases of schizophrenia in 3,035 lifetimes at risk in the control families, and 116 cases of schizophrenia in 2418 lifetimes at risk in the patient families. These translate into average MR of narrowly defined schizophrenia of 0.5% for relatives of controls and 4.8% for relatives of schizophrenics [Kendler and Diehl, 1993].

### Twin Studies: How Large Is the Genetic Component of Risk?

Studies of twins provide a way to estimate the relative importance of shared genetic material and shared environment in the development of a disease (or any other trait). Twin studies of schizophrenia have been reviewed in detail by Cardno and Gottesman [2000]. These show consistent evidence of a genetic effect with higher concordance in monozygotic (≈50%) than dizygotic (≈17%) twins and estimated heritability for the disorder as defined by DSM III [Farmer et al., 1987] or DSM IIIR [Cardno et al., 1999] of close to 80%. Studies of twins also show most clearly that liability to schizophrenia is not completely genetic, and is

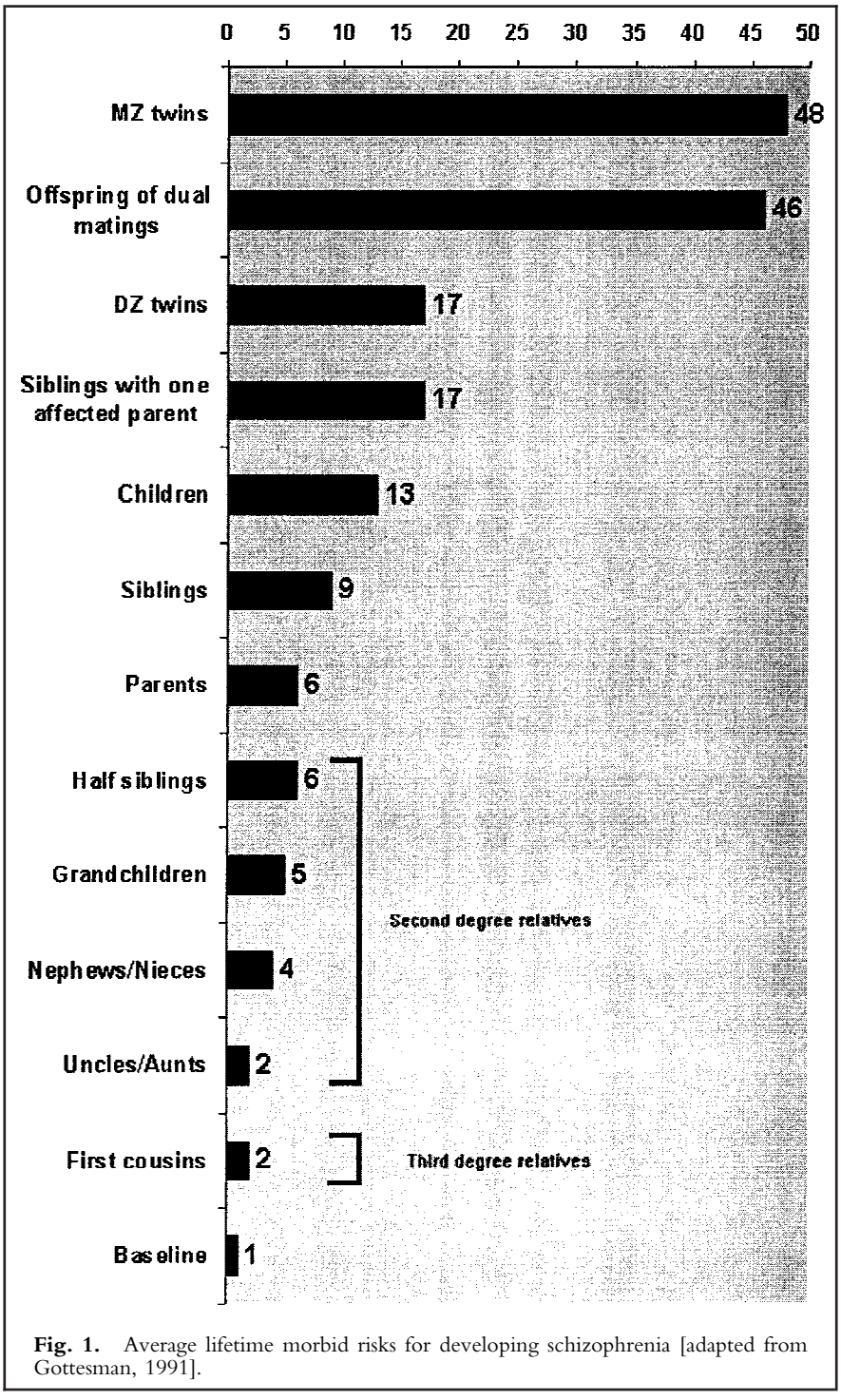


**Fig. 1.** Average lifetime morbid risks for developing schizophrenia [adapted from Gottesman, 1991].

thus a complex trait, determined by genes, environment and their co-action or interaction.

### Adoption Studies: Is Familial Aggregation Due to Shared Environment?

Across all adoption studies performed, the increased risk of schizophrenia was present in the biological relatives of schizophrenics [Prescott and Gottesman, 1993]. In the first study of its kind, Heston [1966] found that the 5 of 47 adopted-away offspring (16.6%) of schizophrenic mothers were schizophrenic compared to 0 of 50 adopted-away offspring of control mothers. In Finland, a much larger study of adopted away offspring of schizophrenic mothers [Tienari, 1991] shows that in 361 families of adopted offspring, 13 of 144 children (9.1%) of schizophrenic mothers have a schizophrenia spectrum disorder and 7 of 144 (4.9%) are schizophrenic, whereas 2 of 178 control offspring (1.1%) are schizophrenic. In studies of adoptees in Denmark, schizophrenia was found to be significantly more common in the biological relatives of schizophrenic adoptees than in the biological relatives of control adoptees in both urban [Kety et al., 1968] and non-urban [Kety et al., 1994] samples. The rates of schizophrenia were low and not different in the adoptive families of both affected and control groups.

### Segregation Analysis: How Is the Genetic Risk Transmitted?

The generalized single locus (GSL) model, commonly used in parametric linkage analysis, assumes that a single gene is responsible for all liability. The multifactorial threshold (MT) model assumes instead a continuum of liability due to additive genetic and environmental factors [see Gottesman, 1991], in the upper reaches of which, a person may become schizophrenic or not and may change over time. An analysis of the data from a carefully selected number of European studies demonstrated that neither the GSL nor MT models are adequate to explain observed patterns of risk [McGue et al., 1985], although the MT model produced a slightly better fit. Although inconclusive for formal hypothesis testing, the results of a mixed model analysis [Vogler et al., 1990] were most consistent with multifactorial inheritance and no major gene.

### Concordance in Extended Families: How Do the Multiple Factors Interact?

Risch defined the quantity $\lambda_R$, the ratio of risks in relatives of type R to the population risk [Risch, 1987]. ($\lambda_R$-1) decreases by a factor of two with each degree of kinship for monogenic or ad-

ditive polygenic traits, and by a factor of more than two for polygenic traits with epistasis. In an epistatic system, genes have a multiplicative interaction and the total liability from *n* genes is greater than the sum of the *n* individual liabilities. The fall-off in concordance rates for a trait in first, second and third degree relatives allows estimation of the number of different genetic loci involved and their interaction type. Data from American schizophrenics and their relatives are most consistent with three to four epistatically interacting loci [Risch, 1990]. Basic modelling with minimal assumptions shows that as the number of loci increases, the risk-bearing alleles at those loci become very common in the population, on the order of 14–20% [Riley et al., 1997a].

Such loci will show smaller effects when examined singly than additively interacting ones, because the proportion of total risk associated with a single locus in an epistatic system is less than that for a single locus in an additive system with the same *n* genes. Such loci must also be biologically related, functionally, temporally or spatially. Epistatic interaction is only possible if the *genotype* (the two alleles, or variable forms, of a gene) or *phenotype* (the observable effect of the genotype) from one gene exert an effect on the genotype or phenotype from another. Modelling such synergistic interaction for hypothesis testing or data analysis is much more complex than modelling additive interaction, because the risk for particular genotypes (also called penetrance) at different loci must be defined, and this requires specifying the loci and genotypes, and their contribution, a priori. At our current stage in studies of most complex genetic traits, where the individual genes contributing to risk are unknown, this is clearly not possible.

***Liability to schizophrenia is a complex trait, determined by genes, environment and their co-action or interaction.***

### Spectrum Disorders: Is Risk for Other Conditions Increased in Relatives of Schizophrenics?

Kendler and Diehl [1993] also reviewed results from studies of other illnesses in relatives of schizophrenics that included personal interviews structured diagnostic criteria from DSM-III or DSM-III-R and blind diagnoses. The results are extremely variable across studies and different conditions examined. In five of seven studies, the risk of schizotypal or paranoid personality disorders (SPD, PPD) in relatives of schizophrenics are consistent at 4–4.5 times that in the control families. Of seven studies (overlapping those above) which meet the same criteria and examine the risk of schizoaffective (SAD), schizophreniform (SD) and delusional disorders (DD), and atypical psychosis (AP) in the relatives of patients, five showed significantly higher risks of these conditions, as well. Two other studies, examining the converse of the question, find that the risk of schizophrenia is significantly higher in the relatives of individuals with SAD and SD than in controls [Kendler et al., 1986, 1993].

Studies of wider spectra of psychopathology, including unipolar (UP) and bipolar (BP) affective illness, anxiety disorder (AD) and alcoholism show more ambiguous results. Six of nine studies examining the risk of affective disorders find no significant difference between relatives of schizophrenics or schizoaffectives and controls, consistent with the generally accepted dichotomy between psychotic and affective illness, but it is important to note that a third of studies do detect excess risk of affective disorders. Five of six studies of risk of AD in relatives find no significant differences. Four of five studies of alcoholism find no significant increase in risk. A twin study that explored the DSM III definition of schizophrenia found evidence of an increased degree of genetic determination when concordance was broadened to include categories such as schizophreniform and atypical psychosis. When co-twins with a broader range of conditions including major depression were included as 'affected', however, the evidence of a genetic effect, as reflected in the monozygotic to dizygotic concordance ratio, fell markedly [Farmer et al., 1987].

## MATERIALS AND METHODS

### Where and How Will Such Genes be Found?

*Diagnostic categories: who is affected?*

Numerous definitions of the phenotype are used in different samples, depending on whether spectrum disorders are included. Narrow diagnostic schemes are those that treat only schizophrenia and schizoaffective disorder as affected. Studies including only schizophrenia will be termed very narrow. Intermediate schemes include the core and narrow spectrum diagnoses (schizotypal personality and all other nonaffective psychoses). Broad schemes include the above plus mood congruent and incongruent psychotic affective illness and paranoid, avoidant and schizotypal personality disorder. Very broad schemes add all other psychiatric diagnoses to those above.

***Data are most consistent with three to four epistatically interacting loci. As the number of loci increases, the risk-bearing alleles at those loci become very common in the population.***

### Analysis Methods: Are We Asking the Right Question?

*Parametric linkage: the LOD score*

Classical Mendelian genetic illnesses are assumed to have a single faulty gene,

located at a single place on a chromosome. Because these illnesses are rare, the rare risk allele must segregate from parents with a family history into affected offspring, or arise as an even rarer de novo mutation. By following the segregation of marker alleles from the affected lineage into offspring, chromosome regions in which affected offspring inherit one marker allele and unaffected offspring the other can be identified. Likelihood based tests can be maximized over one or more parameters, so the focus is often the relative likelihood of one parameter value compared to another, expressed as a likelihood ratio. In LOD score analyses, the likelihood ratio is maximized over $\Theta$, the rate of recombination, that increases with the physical distance between loci. More than one gene can produce the same phenotype, and HLOD analyses are maximized over $\Theta$ and the proportion of families linked to a given locus, $\alpha$.

Recombination in the search for disease genes is an apparent event between real genetic marker alleles and the conceptual alleles 'affected' and 'unaffected'. In real terms what is being examined is whether affected members of a family share one of the two possible alleles they can inherit, and unaffected members the other. Differences between affected individuals or similarities between an affected and an unaffected individual appear in the calculation as recombinations, increasing $\Theta$ artificially. This can be partly overcome by treating all unaffected relatives as unknown, the affected only analysis, but this leaves several problems just in considering the affected members of a family.

First, in a disease with multiple common inputs, no two individuals (even in the same family) need to share input from any individual gene (because there are many genes) or from one particular lineage (because the risk alleles at all these genes are relatively common). Second, this will increase apparent recombination, even in affected only analyses, inflating the apparent distance between marker and disease and making accurate positioning of a putative gene impossible. Third, it will unavoidably decrease the magnitude of the statistic: because the LOD score is the log of a ratio, as the value of $\Theta$ increases toward 0.5, the value of the ratio decreases toward 1, and that of the statistic decreases toward 0. The inescapable conclusion is that whereas parametric linkage analysis is extremely powerful for the monogenic traits it was invented for, much of its power is lost in complex traits. Multipoint parametric linkage analysis, a powerful tool for defining regions of the genome that *do not* contain the single gene responsible for a monogenic trait, has in fact been shown to be statistically invalid for polygenic traits [Risch and Giuffra, 1992].

### Nonparametric Linkage and the NPLZ Score: Allele Sharing in Affected Relative Pairs

Nonparametric methods, based on testing for deviations from expected allele sharing distributions, avoid many of these problems. All classes of relatives have predefined probabilities of sharing zero, one or two marker alleles at a random locus. Statistical tests exist that examine whether the same allele is shared identical by state (IBS) beyond chance expectation. Because marker alleles are *not* the gene of interest, however, it is more compelling to see that affected relatives share alleles inherited from the same source identical by descent (IBD). This method is not ideal, however, because the high population frequency of risk alleles means that they may be inherited from different parents. The most common nonparametric method currently used is a multipoint IBD approach [Kruglyak et al., 1996], that considers all loci simultaneously to examine for excess sharing in affected relative pairs IBD in a multipoint manner. Results of these analyses will be referred to as NPLZ scores throughout. When the data are fully informative, and often they are not, the method specifies exactly which of the distinct founder alleles each individual has inherited at every point in the linear map of marker loci. Two different groups, however, have shown that when data are not fully informative, the NPL test is overly conservative [Davis and Weeks, 1997; Kong and Cox, 1997].

## RESULTS

### Where Is the Evidence Strongest for Schizophrenia Susceptibility Genes?

In reviewing results from studies using molecular genetic markers we have sought to avoid the publication bias in favor of positive results, by including data from meeting abstracts and chromosome workshop presentations (that will be termed preliminary), as well as peer-reviewed, published sources. Given the problems in accurately estimating recombination fractions, the value of $\Theta$ at which the LOD maximizes clearly has little meaning and these are not included in the summary of results. The distances between markers, however, do assist in interpreting whether two results seem to overlap each other, and we have attempted to include this information, either in centimorgans (cM) or in chromosome bands, wherever possible. The number of chromosomes with positive results is large. Several (16 [Shaw et al., 1998], 19 [Kaufmann et al., 1998], 20 [Moises et al., 1995]) have had a single report published, often showing positive results for a single marker, that is less impressive than several reports converging on the same region or positive data across a series of markers. With the exception of chromosomes 3 and 11, the former a focus of much research interest and the latter a rare chromosomal anomaly of potential interest, only those chromosomes with multiple overlapping findings have been included.

### Chromosome 1

Interest in chromosome 1 in schizophrenia began with reports of a balanced 1:11 translocation segregating with serious mental illness in a large pedigree from Scotland [St Clair et al., 1990], although this region was not studied in the same intensive manner as the region around the chromosome 11 breakpoint. The chromosome 1 breakpoint lies at 1q42.1, and two groups reported preliminary suggestive linkage findings in this region. In a three stage genome screen of a population isolate from Finland, data from 20 narrow

definition families in the second stage analysis gave a LOD of 3.73 at D1S2141 (1q32–q41), and 3.27 at D1S491 about 4.5 cM away [Hovatta et al., 1998]. Other markers in the region were also positive. This increased to 3.82 at D1S2891 in the dense-mapping third stage of the genome screen [Hovatta et al., 1999]. The genome screen of 54 narrow definition families in the Maryland sample [Blovin et al., 1998] also gave some preliminary evidence for this region, with an NPLZ of 1.39, $P = 0.084$, at D1S304 (1q44).

At the opposite end of the chromosome, the genome screen of 21 broadly defined African-American families in the Dallas sample gave two positive signals, an NPLZ of 2.18, $P = 0.002$ at D1S3721 (1pter–p21) and 2.13, $P = 0.02$) at D1S3669 (1p35–p32) [Garver et al., 1998]. Nearby, genome screen data from the Oxford/SUNY sample gave an HLOD of 2.40 at D1S196 (1q22–q23) with 46% of the narrow definition families contributing, whereas the maximum NPLZ was 1.86, $P = 0.003$, in the broad definition families at D1S1599 [Shaw et al., 1998]. Findings are summarized in Figure 2.

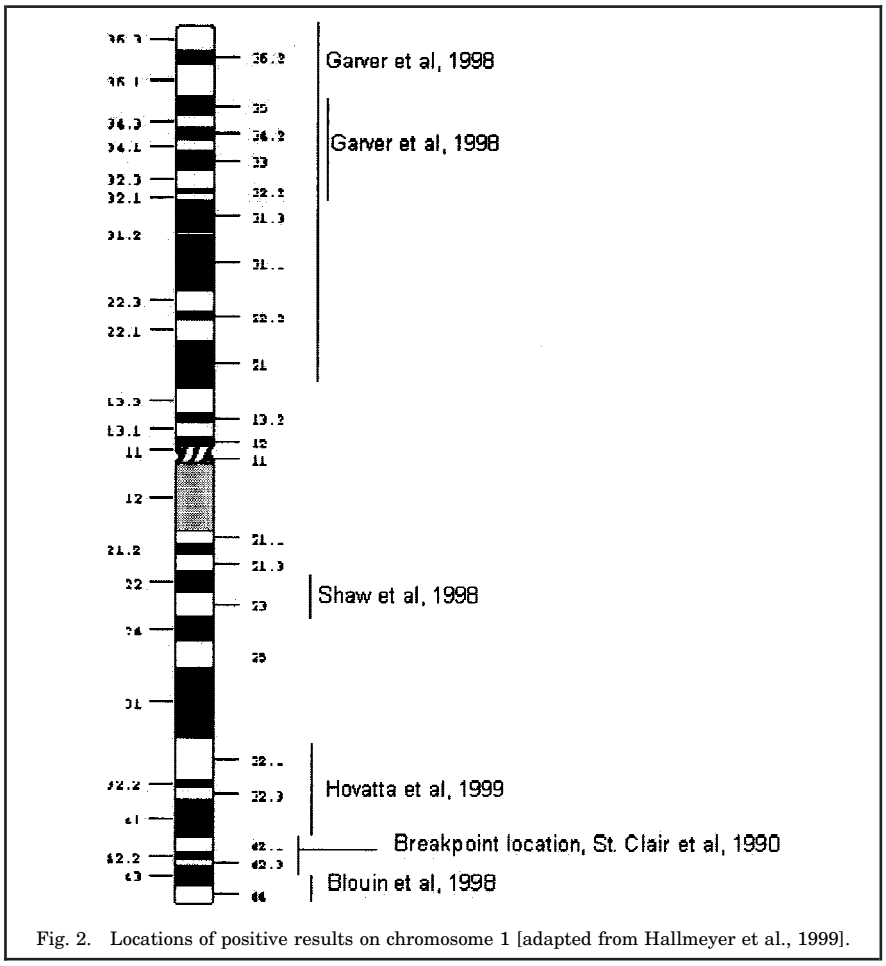


Fig. 2. Locations of positive results on chromosome 1 [adapted from Hallmeyer et al., 1999].

## Chromosome 2p22–q21

Interest in this region of chromosome 2 began with the publication of a single case report of a balanced 2:18 (q21;q23) translocation segregating in a family with schizophrenia [Maziade et al., 1993]. Findings to date are summarized in Figure 3. A follow-up study tested five genetic markers on chromosome 2q21 in 14 Austrian and US families using very narrow (schizophrenia only), intermediate and very broad (including affective disorders) diagnostic schemes [Aschauer et al., 1993]. Data from D2S44 and a very broad diagnostic model gave a LOD of 1.71. In the first stage of a genome screen using narrow definition of the phenotype, data from 5 families from Iceland produced a $P = 0.000001$at D2S135 (2q12–q13) using a weighted pairs correlation test [Moises et al., 1995]. Results this extreme from a nonparametric test in a small sample must be treated with caution [Levinson et al., 1998]. Indeed, in the second round of this genome scan, data from 65 families from Europe, North America and Taiwan gave no evidence for an effect in this region.

Data from three other genome scans gave some positive results, but spread over ≈100 cM of chromosome 2, from 2p22–q21 [Hallmayer et al., 1999]. Data from a mixed sample of 54 families using a narrow disease definition gave an NPLZ of 1.26 ($P = 0.104$) for D2S405 (2p22, ≈90 cM from D2S135) [Blouin et al., 1998]. D2S1337 (2p15–p14, ≈60 cM from D2S135) gave an NPLZ of 2.13 ($P < 0.01$) in data from 70 families containing 100 affected sib pairs using a narrow definition of the phenotype [Shaw et al., 1998]. Genome screen data from marker D2S410 (2q12–q13, ≈7 cM from D2S135) yielded an NPLZ of 2.01 ($P < 0.01$) (one of the two most positive results) in a mixed ethnicity sample of 43 North American and Australian pedigrees under an intermediate diagnostic scheme [Levinson et al., 1998]. In 43 narrow definition American families of European descent, the NIMH/Millenium genome screen detected an NPLZ of 2.41, $P = 0.008$ at marker D2S293, with allele sharing of 63% [Faraone et al., 1998]. Finally, in a study of families with schizophrenia from Palau in Micronesia, a single large pedigree gave a LOD of 2.17 at D2S441 (2p13–p12, ≈40 cM from D2S135) [Coon et al., 1998]. Results for the same marker in a larger set of 16 families were reduced but still positive with a LOD of 1.69. Findings are summarized in Figure 3.

## Chromosome 3p24

In 57 systematically ascertained families from the Maryland family sample [Pulver et al., 1994b], data from marker D3S1283 gave a LOD of 2.34 using a narrow diagnostic model and analyzing data from only affected individuals in

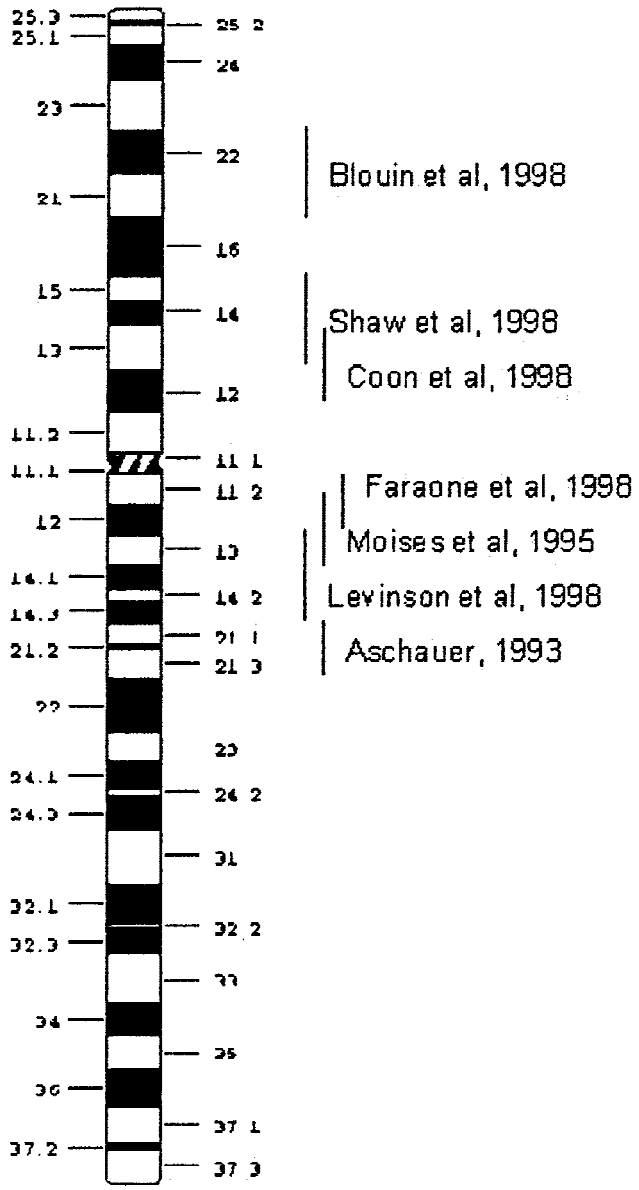


Figure 3. Locations of positive results on chromosome 2 [adapted from Hallmeyer et al., 1999].

the pedigrees [Pulver et al., 1995]. The Schizophrenia Linkage Collaborative Group study, the largest collaborative genetic study of schizophrenia ever undertaken at that point, failed to provide any additional support for this finding [Levinson et al., 1996]. Although reports of excess homozygosity for one allele of a polymorphism in the dopamine receptor D3 gene (located at 3q13) have appeared [Crocq et al., 1992; Williams et al., 1998], no further data implicating chromosome 3p has been published.

### Chromosome 4q24–q32

In the NIMH Genetics Initiative analyses of 30 narrow definition African American pedigrees, a cluster of 3 markers on 4q24–q32 gave some evidence for involvement in liability to schizophrenia. Data from D4S2395 gave a peak NPLZ of 1.68 ($P$ = 0.0492) and data from D4S1644 gave an NPLZ of 1.54 ($P$ = 0.0637) [Kaufmann et al., 1998]. These markers are separated by 17 cM. This region has been the focus of more attention in studies of Bipolar Affective Disorder [Kennedy et al., 1998, 1999]. Several sets of preliminary data have been presented at chromosome workshops over the past two years. In 1997, the following data were presented [Kennedy et al., 1998]. In an analysis where the Irish Study of High Density Schizophrenia Families (ISHDSF) sample was subdivided into three sets of families, only one marker, D4S1644 with an NPLZ of 2.1 ($P$ = 0.0008) under the narrow definition and 2.9 ($P$ = 0.0002) in the very broad definition, gave any evidence for linkage. Data from the genome screen of 43 multiply affected families from the US and Australia gave a peak NPLZ of 1.54 ($P$ = 0.063) at D4S2623, located about 14 cM centromeric to the NIMH Genetics Initiative finding. Two other markers nearer to the NIMH region gave smaller NPLZ scores, D4S1644, NPLZ 1.10, $P$ = 0.136, and D4S1625, NPLZ 1.33, $P$ = 0.094. Preliminary data from an affected sib pair genome screen of 81 families found no evidence for any effect on chromosome 4. In 1998, a further report of preliminary data was made from 72 German and Israeli pedigrees that found an NPLZ of 2.64 for a region of 4q near the centromere [Kennedy et al., 1999]. The study of the Finnish isolated population found a LOD of 2.74 in the region 4q31 at D4S1586 [Hovatta et al., 1999]. Only the finding in the Finnish population is in the same area of the chromosome as the finding from the NIMH African-American families. Data are summarized in Figure 4.

### Chromosome 5

In one of the first linkage studies of schizophrenia ever undertaken, data from 7 families of UK and Icelandic origin gave a LOD of 6.49 using a very broad definition at marker p105–599Ha on chromosome 5q11–q13 [Sherrington et al., 1988]. Numerous replication studies failed to support for this finding [Aschauer et al., 1990] and a combined reanalysis of published data effectively ruled out straightforward linkage heterogeneity [Kennedy et al., 1988; Detera-Wadleigh et al., 1989; McGuffin et

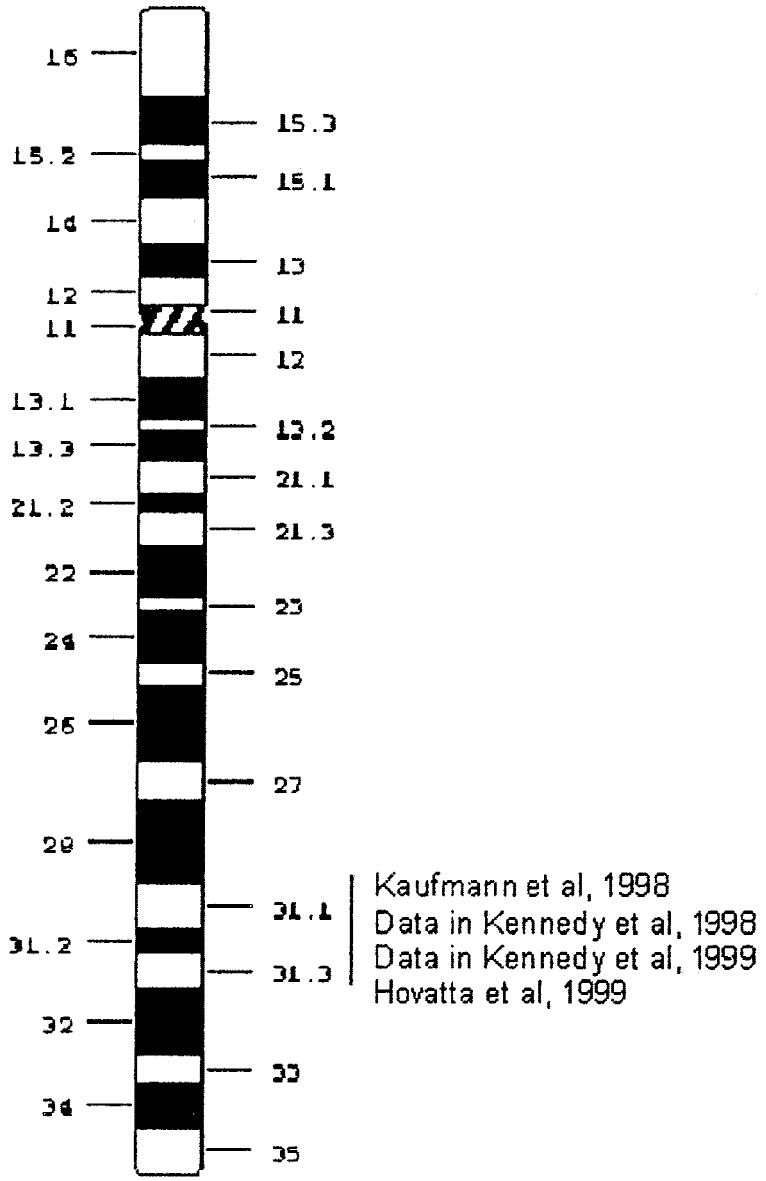


Figure 4. Locations of positive results on chromosome 4 [adapted from Kennedy et al., 1999].

al., 1990; Crowe et al., 1991; Campion et al., 1992; Macciardi et al., 1992].

Recently, however, there has been renewed interest in chromosome 5, although in two separate locations, one close to, and the other distant from, that reported by Sherrington et al. These are shown in Figure 5. Using an intermediate disease definition, data in one large extended pedigree from a sample of 24 nuclear families revealed a LOD of 2.67 for the D5S111 locus (5p14.1–13.1) [Silverman et al., 1996]. Other branches of this pedigree were assessed and the LOD rose to 3.72; using multipoint analysis the LOD rose to was 4.37. Data from the sample as a whole were not positive for this region, and when only schizophrenia was used to define disease, the positive evidence for linkage to D5S111 was greatly reduced. The authors note that over several generations, almost all the ancestors of this extended family could be traced back to a small, relatively isolated, hill region of Puerto Rico. Although the resulting LODs from other markers used were very small, this study did include the most significant marker in the Sherrington et al. study. Preliminary evidence from a genome screen of African American families also suggests a possible locus in this region of chromosome 5 with NPLZ scores of 2.55 ($P = 0.009$) at D5S426 and 2.49 ($P = 0.008$) again at D5S111 [Garver et al., 1998].

Two other groups have also found suggestive evidence of linkage on chromosome 5q22–q31 in a region that seems distinct from either of those in the earlier studies. Data from 265 families in the ISHDSF sample gave an HLOD of 3.04 at D5S393 for the intermediate disease classification using the liability based model [Straub et al., 1997b]. Analyses with a broader disease definition resulted in substantially lower HLODs. Results were positive (though of variable magnitude) across the entire set of 14 markers spanning 45 cM of this region.

Markers in the same region gave positive results first in a sample of 14 families from Germany, with a LOD of 1.8 at a polymorphism in the interleukin 9 (IL9) gene using a narrow disease classification and a dominant model. Then, in a sample of 44 families from Germany and Israel (including 4 from the first sample), data from D5S399, 2 cM from IL9, also gave a LOD of 1.8 using the same analytical structure. This value dropped to 1.27 when the four families common to both samples were removed. Sib pair analyses of the 44 family sample gave evidence for excess allele sharing across a region of 8 cM from D5S666 to D5S658 that includes the markers IL9 and D5S393. Excess allele sharing peaked at 61.5% ($P < 0.005$) for marker D5S399 [Schwab et al., 1997]. Results from another genome screen of 70 pedigrees found an NPLZ of 2.18 ($P < 0.01$) at marker D5S406 using a narrow diagnostic classification [Shaw et al., 1998]. This marker is very poorly mapped, so it remains unclear how this finding relates either to the study of Silverman et al, or to the 5q22–q31 findings. A single case of mental retardation and schizophrenia with a deletion of this chromosome region has also been reported [Karayiorgou et al., 1997]. Preliminary data from the NIMH Genetics Initiative, the US/Australian collaboration, and the Cardiff UK/Wales sib pair study [Crowe et

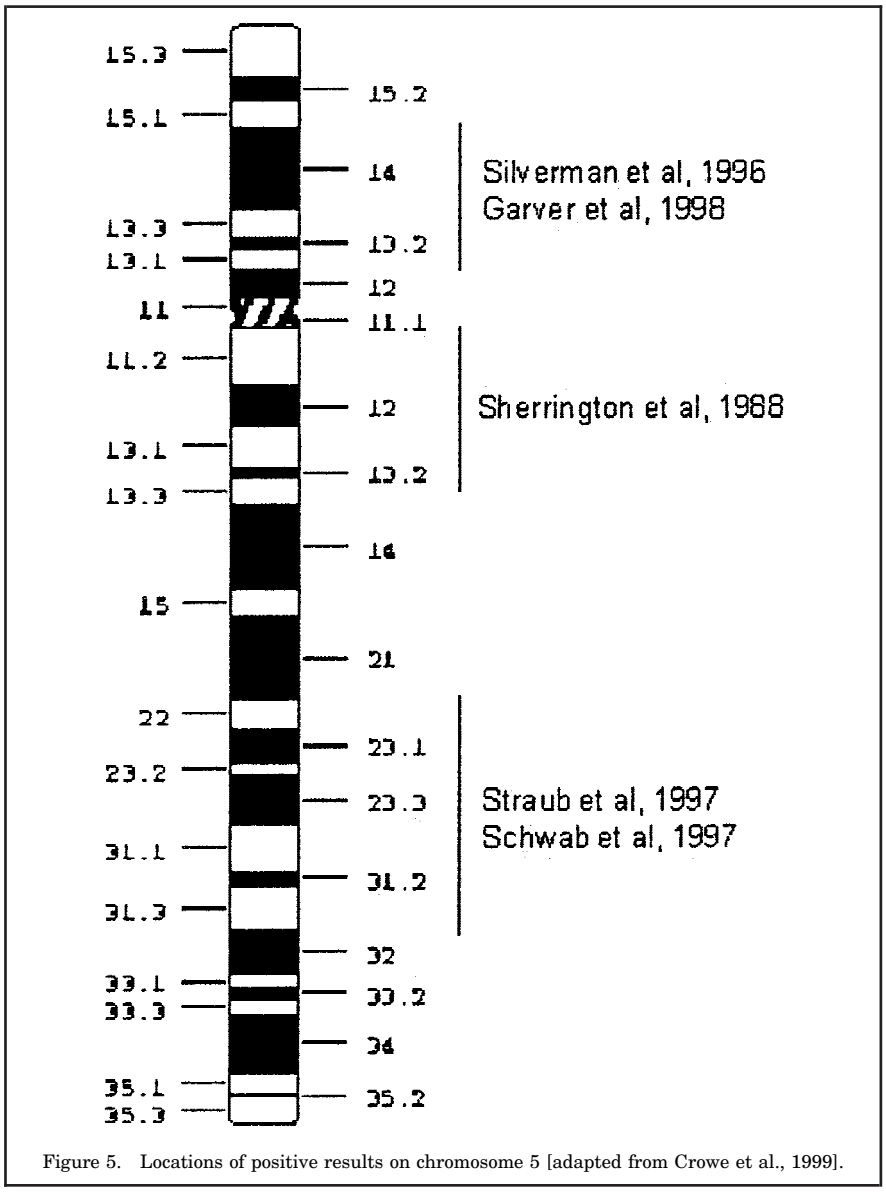


Figure 5. Locations of positive results on chromosome 5 [adapted from Crowe et al., 1999].

al., 1998], the NIMH intramural schizophrenia pedigree collection [Crowe et al., 1999], and published data from another international collaborative study [Moises et al., 1995] found no evidence for a locus on chromosome 5.

### Chromosome 6p24–p22

A detailed regional study of 186 of the 265 ISHDSF pedigrees produced a maximum HLOD of 3.9 in analyses of markers F13A and D6S260, using a model of incomplete penetrance and assuming 50% of families linked [Wang et al., 1995]. Analyses of the entire Irish family cohort using moderately broad diagnostic criteria found a maximum HLOD score of 3.51 with 15% of families linked, 0.4 cM from D6S296 [Straub et al., 1995]. To date, six independent reports of analyses of this region of 6p have been published. Mowry et al. [1995] found strongly negative LOD scores in the region that become very weakly positive only at large values of $\Theta$, using the same model as Wang et al., as well as dominant and recessive models. Gurling et al. [1995] found maximum LOD scores of 0.0–0.214, also at large values of $\Theta$, depending on the model tested, with no evidence for heterogeneity. Riley et al. [1996b] found strongly negative LOD scores across the entire region, although nonparametric tests of allele sharing identical by state (IBS) rather than by descent (IBD) using the Affected Pedigree Member analysis method [Weeks and Lange, 1988] did detect a $t$ statistic of 2.26, empirical $P = 0.026$ based on simulations [Riley and Williamson, 1997].

Antonarakis et al. [1995] found positive HLODs in the region only at large values of $\Theta$ under dominant models, and HLOD maxima of 1.09–1.17 at moderate values of $\Theta$ under recessive models assuming 95–100% of families linked. Schwab et al. [1995] found a multipoint affected sib-pair maximum LOD of 2.2 near D6S274 and −2.0 at D6S296. These studies were all explicit replications that used the same set of markers as reported in the Straub et al. paper [1995]. Moises et al. [1995] analyzing data from a two-stage genome-wide search for schizophrenia susceptibility loci found some evidence for a locus on chromosome 6p, but again found their strongest evidence at D6S274. The Schizophrenia Linkage Collaborative Group study, attempting to replicate findings on chromosomes 3, 6 and 8, examined the region 6p24–p22 and contained data from most of the samples of schizophrenia families held around the world, including those above and found some support for a susceptibility locus in this region. Across the set of markers tested, allele sharing of 55.9% and a multipoint maximum likelihood score (MLS) of 2.19, $P = 0.001$, was found at in the replication sample only, and 2.68, $P = 0.0004$ in the replication sample plus the ISHDSF families [Levinson et al., 1996]. This analysis method is similar to the NPLZ test, but is an earlier version [Kruglyak and Lander, 1995]. It is also of interest to note that eye tracking dysfunction, a widely used secondary phenotype for schizophrenia, has been mapped to chromosome 6p in this same region of interest [Arolt et al., 1996]. Data from both chromosome 6p and 6q are summarized in Figure 6.

McGuffin and Sturt [1986] reviewed linkage and association results from the 'pre-molecular' era of classical genetic markers. The most consistent result was an association with the histocompatibility allele HLA-A9, found in 7 out of 9 studies, but this finding

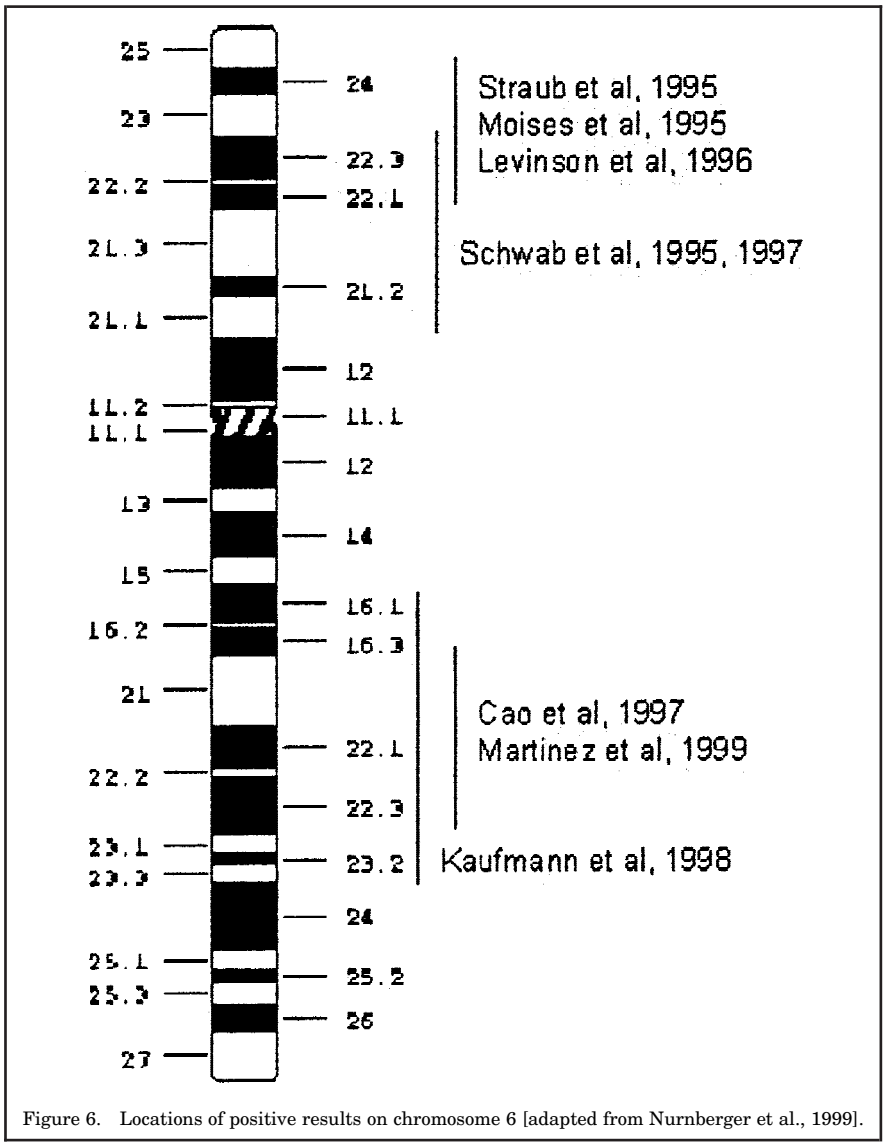


Figure 6. Locations of positive results on chromosome 6 [adapted from Nurnberger et al., 1999].

was complicated in a number of ways. Positive results were found only for paranoid subtypes of schizophrenia and there was no overall support from linkage studies [McGuffin et al., 1983]. Recent studies, although not ruling out a role for HLA, have tended to focus on other components of the HLA complex and on potential mediating mechanisms such as susceptibility to viral infections in utero [Wright et al., 1998]. The findings are nevertheless of some interest in view of the results on chromosome 6p.

### Chromosome 6q

A sample of 53 US families of mixed ethnicity containing a total of 81 affected sib pairs provided evidence for a susceptibility locus on chromosome 6q21–q22.3 [Cao et al., 1997]. This study is unique in that a second independent sample of families held by the same researchers was used to replicate the finding internally. In the first sample, marker D6S416 showed the greatest degree of excess allele sharing among affected siblings at 69% shared IBD ($P = 0.00024$). In the replication data set, 69 families containing 109 affected sib pairs gave maximum IBD allele sharing of 64% ($P = 0.0004$) at D6S424, 62% ($P = 0.0009$) at D6S283 and 63% ($P = 0.0009$) at D6S423. A total of 7 markers spanning approximately 3.5 cM gave sharing between 55 and 65%, and $P$ values <0.04. A follow-up study by the same group found positive but less significant maxima using a third independent sample, where D6S424 showed 62% IBD sharing ($P = 0.022$) [Martinez et al., 1999]. Combining the data from both replication samples, the interval between D6S424 and D6S301 gave a LOD of 3.82 and IBD sharing of 63.8% ($P = 0.000014$). Data from the African-American pedigrees in the NIMH/Millenium schizophrenia genome screen also provided support for these findings. D6S1009 gave an NPLZ of 1.89 ($P = 0.032$) and D6S1056 gave an NPLZ of 1.56 ($P = 0.062$) [Kaufmann et al., 1998]. These two markers are approximately 37 cM apart, and flank the region of interest identified by Cao et al.; intervening markers in the NIMH/Millenium genome screen gave small positive NPLZ scores, though not of the same magnitude as these two markers. No new preliminary linkage data has been presented in the last two years [Nurnberger Jr. et al., 1998, 1999].

### Chromosome 7

Before 1998, there had been no reports of suggestive linkage findings on chromosome 7 and the data that follow are not the most significant findings in either study. The close positioning of these two results, however, makes them worthy of mention. In the genome screen of the narrowly defined Maryland family sample, D7S2212 (q21.1–q21.3) gave an NPLZ of 2.5, $P = 0.007$ [Blouin et al., 1998]. The NIMH/Millenium European American sample also provided suggestive peaks at two contiguous markers, an NPLZ of 1.66, $P = 0.05$ at D7S821(q21.3–q22) and 1.74, $P = 0.04$, at D7S1799 (q22) [Faraone et al., 1998]. These three markers are spread over approximately 30 cM of the chromosome, and are summarized in Figure 7.

### Chromosome 8p22–p21

Again in the Maryland family sample, Pulver et al. [1995] reported findings of very significant excess allele sharing and small positive LOD scores from their continuing genome scan on chromosome 8p22–p21. Across a region of 10 cM containing 6 markers, affected sib-

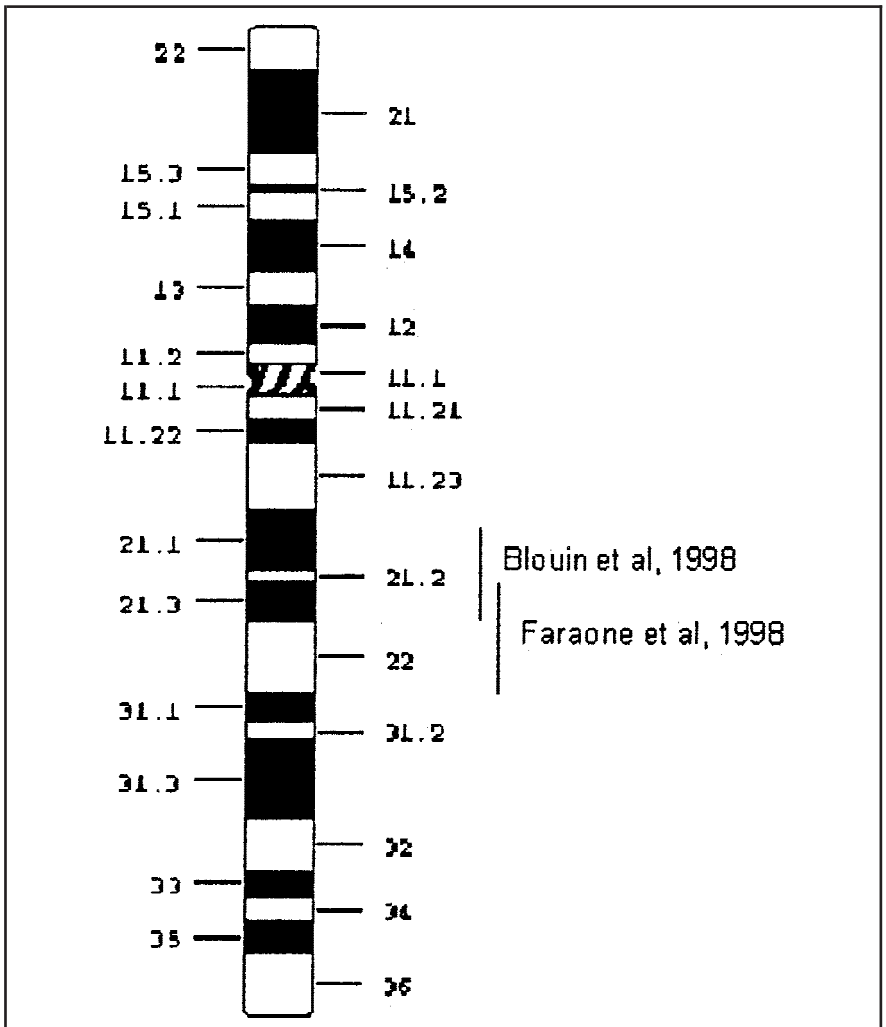


Figure 7. Locations of positive results on chromosome 7 [adapted from Hallmeyer et al., 1999].

pair analysis gave *P* -values of between 0.00004 (D8S258) and 0.0097 (LPL). Parametric analysis yielded a maximum LOD score of 2.35 under a dominant model and 2.2 under a recessive one examining data from affected pedigree members only. The Schizophrenia Linkage Collaborative Group study found an HLOD of 2.22 at marker D8S261 in the new samples only, and 3.06 when the Maryland families were included, both under a recessive model [Levinson et al., 1996]. Allele sharing (again using the multipoint maximum likelihood method) was higher in the original Maryland families alone at 70.4% shared (MLS = 2.90, $P$ = 0.0002) than in the replication samples (54.1%, MLS = 1.58, $P$ = 0.005) or the combined data (55.3%, MLS = 2.73, $P$ = 0.0003). Preliminary data from a denser map of markers in the Maryland sample showed an HLOD of 5.12 with 58% of families linked and an NPLZ of 3.73, $P$ = 0.00014 at marker D8S1820, close to the end of the original region of interest in this sample [Dombroski et al., 1997]. Data from 21 narrowly defined Canadian pedigrees gave a LOD of 3.49 at marker D8S136, but this decreased to 2.13 in a multipoint analysis [Brzustowicz et al., 1999]. Findings are summarized in Figure 8.

### Chromosome 9q34.3

Data from the South African Bantu family sample gave modest positive LOD and NPLZ results on chromosome 9q34.3, where analyses of affected individuals only gave an HLOD of 0.876 at marker D9S1838 [Riley et al., 1997a]. Simulation studies of the sample indicated that the probability of a LOD of this magnitude for an unlinked marker was between 0.1 and 2.0%. The same marker also gave an NPLZ of 1.42, $P$ = 0.056. Data from the African American families in the NIMH/Millenium genome screen study also yielded positive peaks for 3 consecutive markers spanning 15 cM on chromosome 9q34.3. D9S1825 gave an NLPZ of 1.91, $P$ = 0.0306; D9S1830 gave an NPLZ of 2.17, $P$ = 0.0167; D9S1818 gave an NPLZ of 2.04, $P$ = 0.0272 [Kaufmann et al., 1998]. D9S1830 is 21 cM centromeric of D9S1838. This region is contains two genes of potential interest, dopamine beta-hydroxylase (DBH) and the central subunit of the NMDA receptor (NR1). The first of these has been tested directly: data from 3 markers (including a polymorphism in DBH) in 34 Austrian families gave no evidence for linkage to schizophrenia [Meszaros et al., 1996]. Both collected older data [Moghaddam, 1994], however, and recent transgenic mouse studies [Mohn et al., 1999] support a possible role for NR1 in liability to schizophrenia.

Results of two other studies also suggested a possible chromosome 9 locus, though in very different positions. Data from a two round genome screen, first in 5 Icelandic families and then in 65 mixed ethnicity families showed excess allele sharing on chromosome 9. In the larger sample, allele sharing at D9S175 gave $P < 0.01$ [Moises et al., 1995]. D9S175 is approximately 70 cM from D9S1838. The US/Australia genome screen also gave some evidence for a chromosome 9 locus, finding an NPLZ of 1.54, $P < 0.05$, at D9S257, in a similar position to D9S175, approximately 76 cM from D9S1838 [Levinson et al., 1998]. The genome scan results from the Finnish isolate also show some support for this region, a LOD of 1.95 under a dominant, high penetrance model [Hovatta et al., 1999]. Previous interest in this region, near the centromere, was due to reports of relatively frequent pericentric inversions of chromosome 9 in schizophrenics [Nanko et al., 1993]. Chromosome 9 findings are summarized in Figure 9.

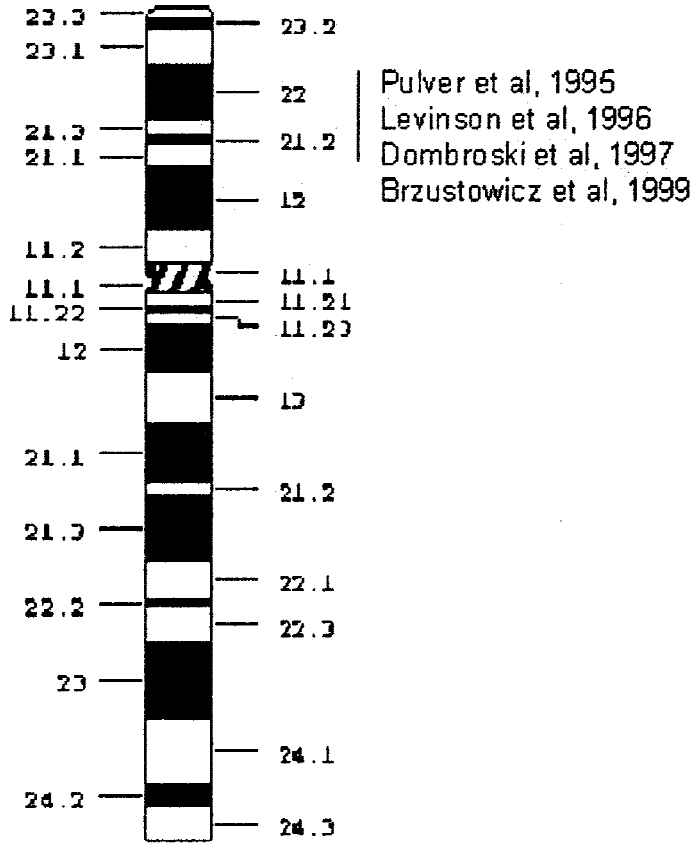


Figure 8. Locations of positive results on chromosome 8 [adapted from Wildenauer et al., 1999].

### Chromosome 10p

The NIMH/Millenium genome screen of 43 US families of European descent produced the most suggestive finding on chromosome 10p15–q21 [Faraone et al., 1998]. Across a set of 9 markers, NPL Z-scores were consistently above 2.0 ($P$ values <0.03), with a peak score of 3.36 ($P = 0.0004$) at D10S1423. Data from the ISHDSF sample also suggested linkage of schizophrenia to this same region [Straub et al., 1998]. Initial data analyses of a subset of 88 families yielded an HLOD of 3.2 ($P = 0.0004$) for marker D10S674. Subsequently, 12 markers spread across 32 cM of this region were analyzed in the entire set of 265 families. In the intermediate diagnostic category, HLODs peaked at 1.95, $P = 0.005$, for D10S2443 under the recessive model and were between 1.56 and 1.77 for other models tested. Nonparametric analyses gave peaks at D10S674 (NPLZ = 1.5, $P = 0.06$) and D10S2443 (NPLZ = 1.47, $P = 0.007$). Nonparametric analyses in a sample of 72 German and Israeli families using a narrow diagnostic category provided further evidence for a susceptibility locus in this region. Markers D10S582 and D10S1423 gave, respectively, 61.5% allele sharing, $\chi^2 = 7.6$, $P = 0.0058$, and 59% allele sharing, $\chi^2 = 4.76$, $P = 0.029$. Using only independent sibling pairs gave 59% sharing, $\chi^2 = 4.17$, $P = 0.041$, for D10S582 and 58% sharing, $\chi^2 = 2.93$, $P = 0.087$, for D10S1423. The maximum NPLZ was 3.2, $P = 0.0007$ for marker D10S1714 [Schwab et al., 1998]. All of the markers are within 5 cM of each other [Wildenauer et al., 1999], and these results are unusual and particularly exciting because of the close agreement in location shown by different samples using different diagnostic and analytical approaches. Results from these three studies are shown in Figure 10.

### Chromosome 11q

Chromosome 11q contains both the dopamine D2 receptor gene (DRD2) and the other breakpoint in the balanced 1:11 translocation reported in a large pedigree from Scotland [St. Clair et al., 1990]. Numerous studies of the region were undertaken and gave no evidence for linkage in other family samples [Gill et al., 1993; Su et al., 1993; Zhe Wu et al., 1993; Mulcrone et al., 1995; Kalsi et al., 1995a]. It seems likely that the effect of the translocation, and the disruption of surrounding genes, is specific to this large pedigree, and not a common susceptibility factor in schizophrenia, but the characterization of the disrupted genes may identify sequences or gene families relevant to more common psychoses.

### Chromosome 13q

Data from a mixed sample of 11 UK and 2 Japanese families initially suggested the possibility of a schizophrenia susceptibility locus on chromosome 13q14.1–q32 [Lin et al., 1995], already an area of interest due to the presence of the 5HT2A receptor gene [Williams et al., 1997]. Marker D13S119 gave an HLOD of 1.62 with 95% of families suggesting involvement of a gene in the region. Preliminary data from two other groups gave some initial support. A LOD of 2.54 was found at D13S128 under a dominant model, and one of 2.53 at D13S779 under a recessive model, in the narrowly defined Maryland families [Antonarakis et al., 1996]. Data from the UK/Icelandic sample gave a LOD of 1.09 at D13S144 with 45% of families possibly linked using an intermediate disease classification [Kalsi et al., 1996].

A further study by the original group using an independent sample of 34 Taiwanese and 10 UK families yielded negative LOD scores over most of the region, except for marker D13S122, that gave a LOD of 1.06 under a dominant model using broad diagnostic scheme [Lin et al., 1997]. When data from both samples were combined and families of European and Asian origin were analyzed separately, however, the European pedigrees gave an HLOD of 1.41 at marker D13S119 with 100% of families suggesting involvement and 1.54 at marker D13S128 with 30% of families suggest-

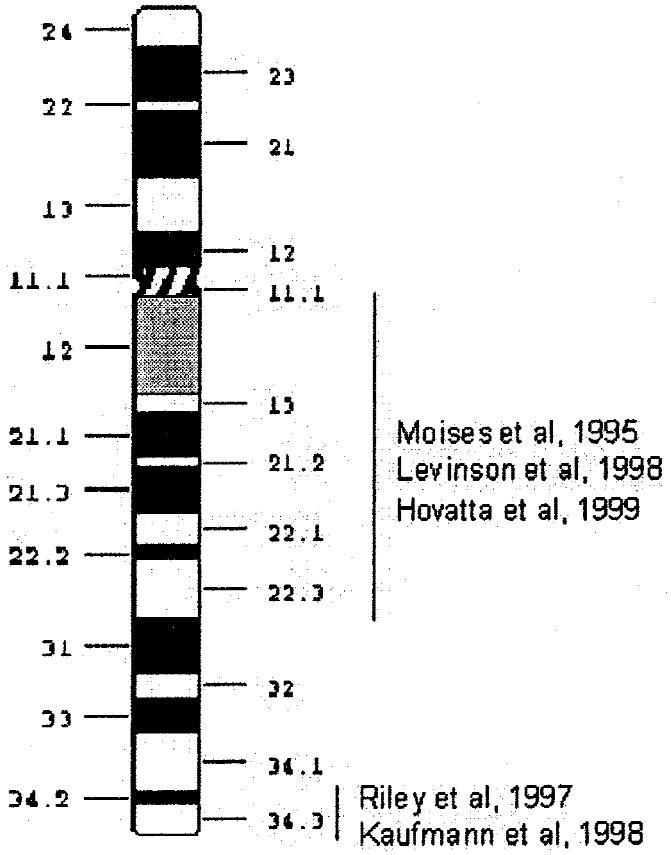


Figure 9. Locations of positive results on chromosome 9.

ing involvement. A multipoint, model free (MFLOD) analysis [Curtis and Sham, 1995] of the European sample yielded a LOD of 2.58 around the markers D13S119 and D13S128, located at 13q32. Positive LOD and MFLOD scores were found around these two markers, but they were separated by a region, centered on D13S121, where the values of both statistics dropped almost to zero.

Genome screen data from 70 families containing 100 affected sib pairs gave a LOD of 2.85 and an NPLZ of 1.8 ($P < 0.001$) at D13S1293, located approximately 40 cM telomeric of D13S119, and more than 50 cM telomeric of D13S128 [Shaw et al., 1998]. Data from other genome screens and replication studies gave mixed results. Analyses of 15 South African Bantu families gave small positive LOD and NPLZ scores across the region examined by Lin et al. [Riley et al., 1998]. Data from 275 of the ISHDSF families gave a LOD of 1.36 under a recessive model at D13S779 close to the positive region reported by Lin et al., but nonsignificant NPLZ results across the region [Straub et al., 1997a]. Data from 9 US families of European descent gave strongly negative LOD scores across a set of 17 markers spanning the whole of chromosome 13 [Jensen et al., 1998]. Genome screen data from a mixed sample of 54 families using a narrow disease definition gave an HLOD of 1.84 with 44% of families suggesting involvement under a dominant model and 3.19 in 48% of families under a recessive model, and an NPLZ of 4.18 ($P = 0.00002$) at D13S174 [Blouin et al., 1998]. Expanding this sample to 105 mixed ethnicity families gave a peak NPLZ of 2.36 ($P = 0.007$) at D13S779, 7 cM from the peak marker in the first analysis. At the 1998 World Congress on Psychiatric Genetics Chromosome 13 workshop, preliminary data from another sample of 76 US families gave no positive results in the region [Barden et al., 1999]. Recently, 3 point analyses using pairs of adjacent markers in a sample of 21 narrowly defined Canadian pedigrees gave an HLOD of 4.42 with 65% of families linked at marker D13S793 [Brzustowicz et al., 1999]. Findings on chromosome 13 are summarized in Figure 11.

### Chromosome 15q13–q14

The first evidence for a possible chromosome 15 schizophrenia susceptibility locus was the report of linkage of the p50 sensory gating deficit (an evoked potential abnormality that is common in schizophrenics and relatively rare in controls, and that segregates as a single gene trait in families) to chromosome 15q13–q14 [Freedman et al., 1997]. In 9 Utah families, D15S1360, that is within 500 kilobases (kb), or 0.5 cM, of the α7 nicotinic cholinergic receptor subunit gene (CHRNA7), gave a LOD of 5.3 when tested against the sensory gating phenotype, and 1.33 when tested against schizophrenia. This gene is an attractive candidate because of the high incidence of smoking in schizophrenics [De Leon et al., 1995], because both nicotine [Adler et al., 1993] and clozapine [Nagamoto et al., 1996] ameliorate the sensory gating deficit, and because a secondary phenotype common in schizophrenics is strongly linked to this region.

Data from South African Bantu families in a dense map of markers at 1 cM intervals around D15S1360 showed some evidence in support of this finding, with positive NPLZ results across the entire map [Riley et al., 1997b]. There were two maximum peaks, one at D15S1043 ($Z = 1.79$, $P = 0.038$) centromeric of the partial duplication of CHRNA7 [Gault et al., 1998] and D15S1360 ($Z = 1.725$, $P = 0.044$) centromeric of CHRNA7 itself. Extended transmission disequilibrium testing (ETDT, [Sham and Curtis, 1995]) gave an allele-wise and genotype-wise chi-square of 6.59 (2 and 3 df, $P = 0.037$) for D15S1360. Analyses with TRANSMIT [Clayton, 1999; Clayton and Jones, 1999] gave evidence for haplotype transmission disequilibrium with

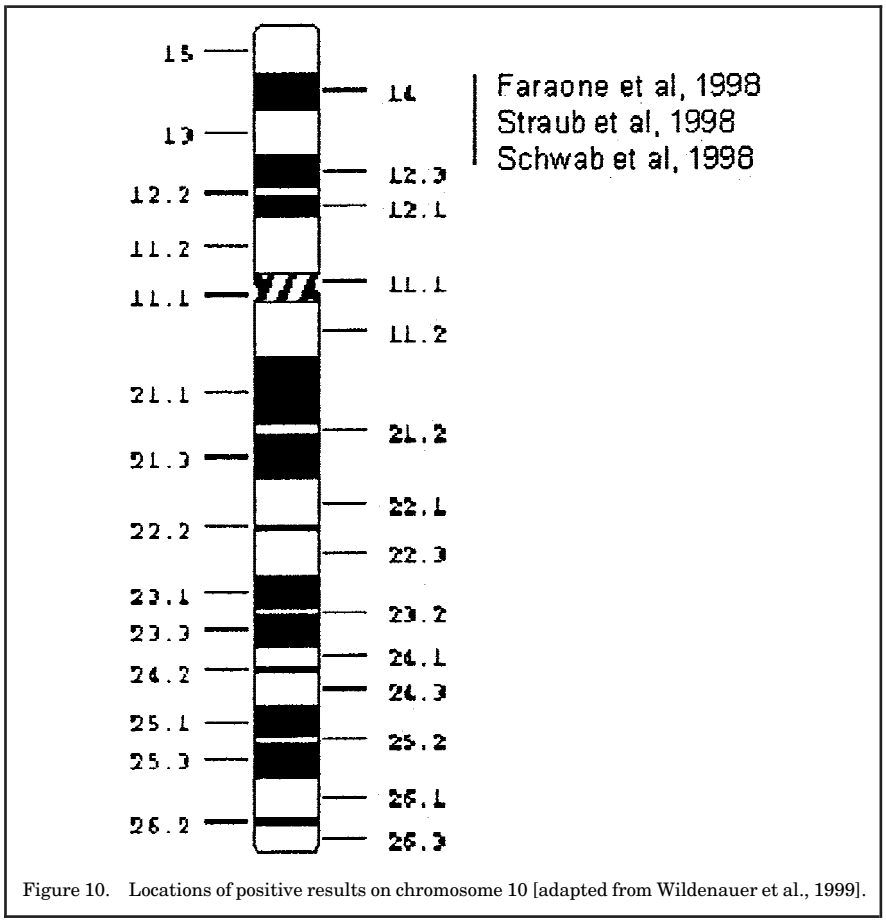


Figure 10. Locations of positive results on chromosome 10 [adapted from Wildenauer et al., 1999].

a global chi-square of 10.647 (4 *df*, $P = 0.007$) and a maximum chi-square of 6.567 (1 *df*, $P = 0.004$) for markers D15S1043 and D15S1360 [Riley et al., in press]. Analyses by the original group in an independent sample showed 58% IBD allele sharing, $P < 0.0024$) at D15S1360 [Leonard et al., 1998]. Two studies have failed to find any evidence for involvement of this locus in 5 families from eastern Canada [Neves-Pereira et al., 1998] and 54 families from the Maryland sample [Curtis et al., 1999]. Data from chromosome 15 are summarized in Figure 12.

### Chromosome 18

Initial interest in chromosome 18 began with several reports of the co-occurrence of psychiatric disorders and chromosomal anomalies [Bassett, 1992; Calzolari et al., 1996; Smith et al., 1996; Mors et al., 1997], and was strengthened by the initial report of linkage between this chromosome and BP [Berrettini et al., 1997]. Data from chromosome 18 in schizophrenic families comes partly due to the inclusion of data from all chromosomes in whole genome screens, and partly from replication attempts, due to the possible overlap between BP and schizophrenia. Two initial replication attempts after the putative BP linkage, in 32 families from the Oxford/SUNY sample [DeLisi et al., 1995] and 9 families from the Utah sample [Fang et al., 1995], gave no evidence of linkage between schizophrenia and chromosome 18. In contrast, preliminary data from the 32 families in the German/Israeli sample gave a LOD of 3.1 at D18S53 when both schizophrenics and affective disorder cases were included in the analysis, and 2.07 at GNAL (18p11.2) using the schizophrenics alone [Wildenauer et al., 1997]. In allele sharing analyses, D18S53 gave $P = 0.0043$ for the schizophrenics alone, and $P = 0.0006$ when the affective disorder cases were included. Transmission disequilibrium studies of the 124 base pair (bp) allele in a polymorphism in the alpha subunit of the olfactory G-protein (GOLF) showed 41 transmitted and 13 non-transmitted ($P = 0.0007$) considering

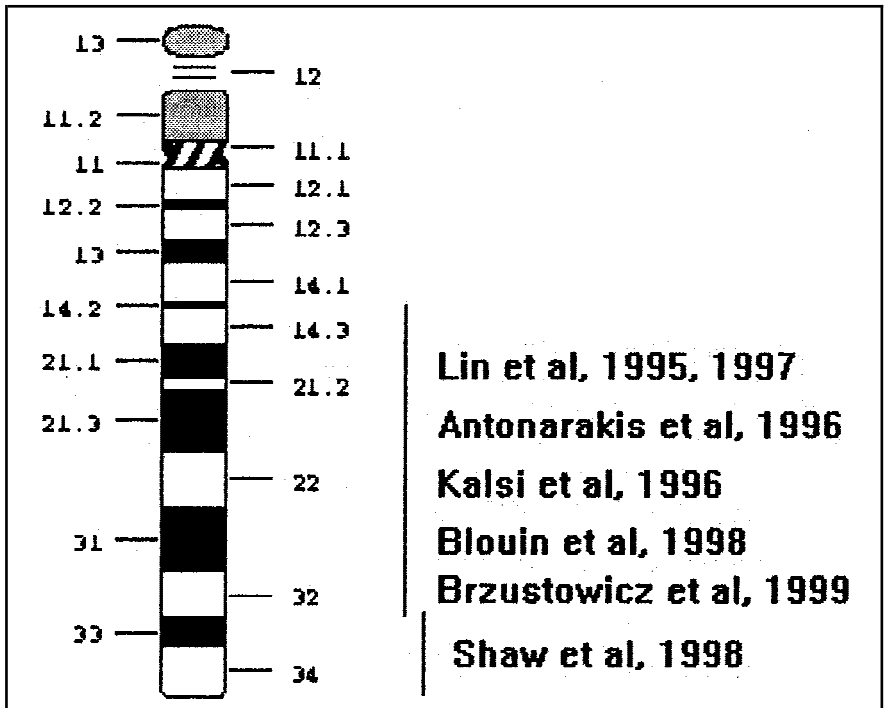


Figure 11. Locations of positive results on chromosome 13.

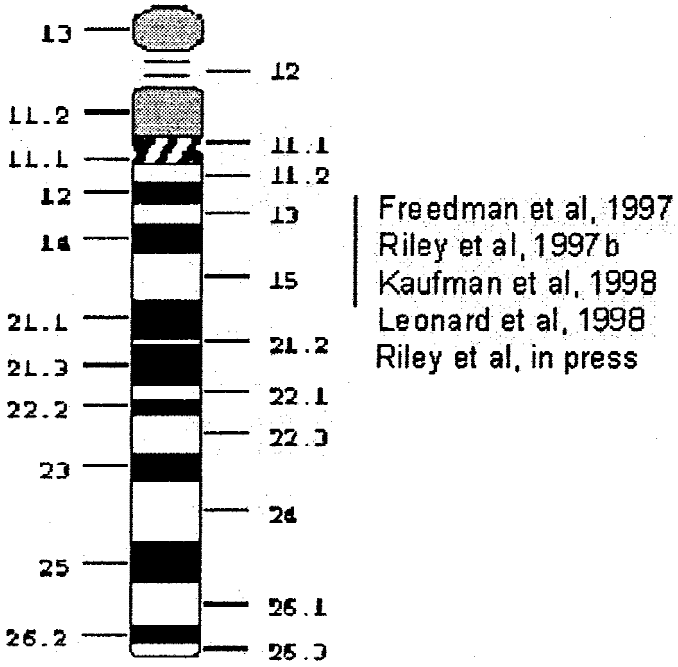


Figure 12. Locations of positive results on chromosome 15.

schizophrenia and schizoaffective disorder, and 45 transmitted and 13 non-transmitted ($P = 0.00012$) when the affective disorder cases were included. Preliminary data from the 81 families in the Cardiff study gave several suggestive positive NPLZ scores, one of them at D18S53 [Williams et al., 1997] and the other at D18S450 (18q21.1). None of the other genome screen samples reported any evidence of linkage to this chromosome [Van Broeckhoven et al., 1998; Van Broeckhoven et al., 1999]. Findings from chromosome 18 are summarized in Figure 13.

### Chromosome 22q

Several reports from independent samples initially suggested that loci at chromosome 22q12–q13.1 might be linked to susceptibility to schizophrenia, with the result that this small chromosome has been one of the most intensively studied for putative schizophrenia susceptibility genes. Early results in the first 39 families of the narrowly defined Maryland sample gave a LOD of 1.54 at the IL2RB marker on 22q13, that increased to 2.82 after maximizing the LOD score over several parameters [Pulver et al., 1994b]. In the full sample of 57 families, the strongest results occurred at CRYB2, 11 cM centromeric of IL2RB, where allele sharing analysis gave a *P*-value of 0.009 [Lasseter et al., 1995]. In 9 narrowly defined families from Utah, first round genome screen data produced a LOD of 1.45 at D22S84 (22q13–qter, 6 cM telomeric of IL2RB) under a recessive model [Coon et al., 1994b]. Further analyses of these families with a dense map of markers across the region yielded a LOD of 2.09 for marker D22S276, 1 cM telomeric of IL2RB, also under a recessive model [Coon et al., 1994a]. Data from 105 narrowly defined families from the US and UK gave strongly negative LOD scores across a set of 10 markers including those described above, although non-parametric tests of allele sharing identical by state (IBS) [Weeks and Lange, 1988] gave a *t* statistic of 2.31, $P = 0.014$, for D22S278, about 0.5 cM centromeric of IL2RB [Polymeropoulos et al., 1994].

A collaboration involving four centres, and containing 256 pedigrees from Europe and the US, examined 3 loci on 22q12–q13, and found negative LODs across this set, both in the total and the individual samples [Pulver et al., 1994a]. A large collaborative study using non-parametric analysis on the combined samples of 11 different groups found 252 alleles shared versus 188 not shared ($\chi^2 = 9.31$, $P = 0.001$) at D22S278 in the 292 complete sib pairs available [Gill et al., 1996]. Using the relationship between excess proportion of alleles shared IBD and the parameters of a single locus model [Suarez et al., 1978], however, the authors conclude that it is likely to be responsible for no more than 2% of the total variance in liability for schizophrenia.

Further reports concerning this region have continued to appear, both direct replication attempts and data from other genome screens. In the UK/Welsh family sample, D22S278 gave a

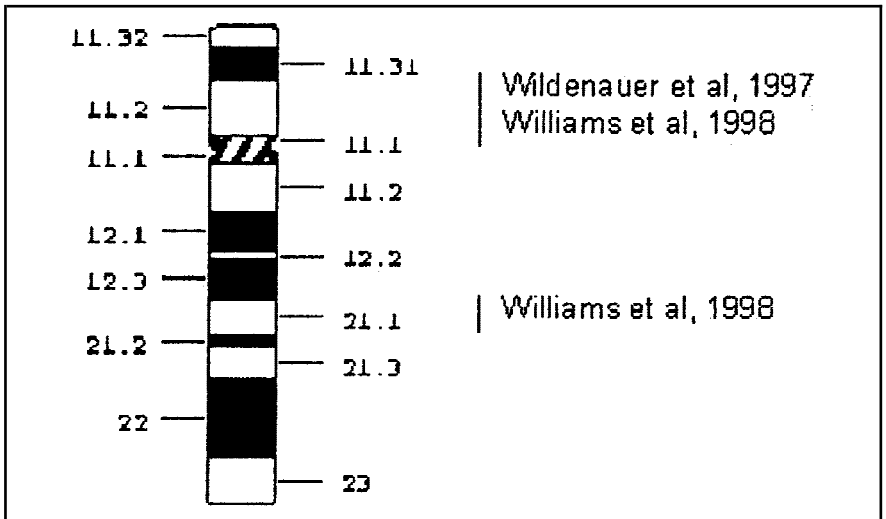


Figure 13. Locations of positive results on chromosome 18.

LOD of 1.51 under a recessive model, and a modest excess of shared alleles in affected siblings ($P < 0.01$) was found for both D22S278 and D22S283 [Vallada et al., 1995]. Results of both parametric and nonparametric analyses of data from D22S283 and D22S274 (0.3 and 3 cM telomeric of D22S278, respectively) in the UK/Icelandic family sample gave no evidence for linkage in the region [Kalsi et al., 1995b]. Data from the South African Bantu family sample gave strongly negative LOD scores across a set of 9 markers spanning the region of interest [Riley et al., 1996a]. In the genome screen data from the Oxford/SUNY sample, D22S446, located 13 cM centromeric to D22S278, gave an NPLZ of 2.16, $P = 0.01$, and positive though less significant NPLZ scores were seen for 4 markers spanning 28 cM around D22S278 [Shaw et al., 1998]. Neither the US/Australia family study [Levinson et al., 1998] nor the ISHDSF [Straub et al., 1997a] found any evidence of even suggestive magnitude in the region. Preliminary data from the 72 pedigrees in the Bonn family sample gave an NPLZ of 1.91 at D22S280 (5 cM telomeric of D22S278) [Hallmayer et al., 1998], consistent with the preliminary report a year before showing a LOD of 1.1 in a subset of 54 families [Zill et al., 1997].

Velo-cardio-facial syndrome (VCFS, including Di George Syndrome) is associated with haploinsufficiency of genes at chromosome 22q11 due to sub-microscopic deletions [Kelly et al., 1993], and it was noted that early linkage results for schizophrenia were near this region [Pulver et al., 1994b]. Ten percent of VCFS patients present with a psychotic phenotype [Shprintzen et al., 1992]. This region also contains the gene for the soluble form of catechol-O-methyl transferase (COMT) located at 22q11, that has been suggested [Dunham et al., 1992] to be involved in the psychiatric symptoms observed in VCFS, and that is known to be functionally as well as genetically polymorphic [Weinshilboum and Raymond, 1977]. In studies of VCFS patients, rates of schizophrenia or schizoaffective disorder from 25–29% have been found [Pulver et al., 1994c; Murphy and Owen, 1997]. Results from chromosome 22 are summarized in Figure 14.

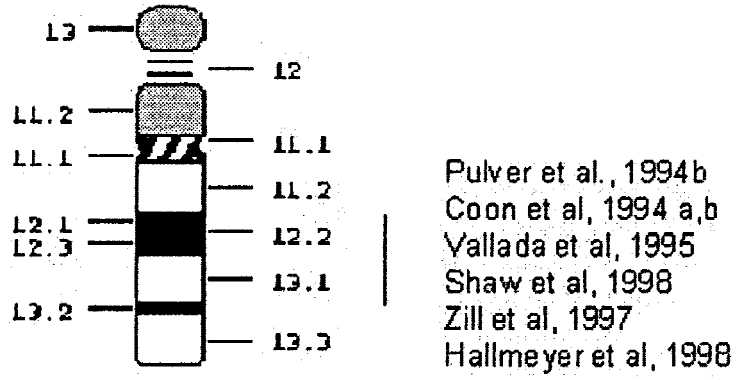


Figure 14. Locations of positive results on chromosome 22.

## X Chromosome

The X chromosome was initially hypothesized as a potential source of genetic liability due to the well documented differences between the genders for various aspects of schizophrenia, including higher concordance in same-gender twin pairs, age of onset (that is generally lower in males) and the greater risk if a female, rather than a male, relative is affected [reviewed by Crow, 1988]. A pseudoautosomal locus for a schizophrenia susceptibility gene that would account for these differences

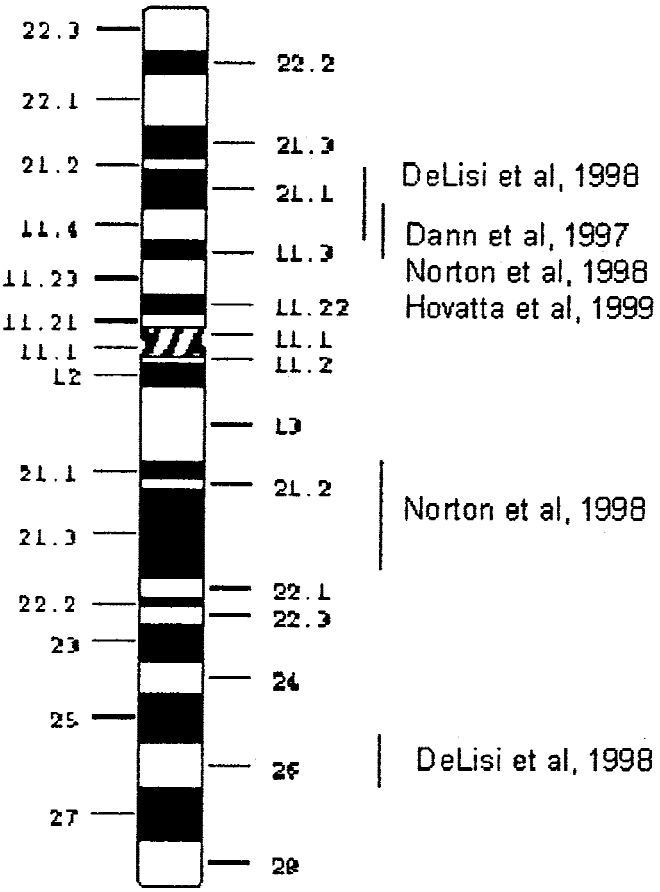


Figure 15. Locations of positive results on chromosome X [adapted from Paterson et al., 1999].

was suggested [Crow et al., 1989]. An early study using sib pair analysis reported evidence of excess sharing at DXYS14 [Collinge et al., 1991], that was supported in one nonparametric replication [D'Amato et al., 1992], but was not supported by a number of other studies using both parametric and nonparametric analyses [Asherson et al., 1992; Wang et al., 1993; Crow et al., 1994; Barr et al., 1994; Maier et al., 1995; Kalsi et al., 1995c].

A large collaborative study examining markers within band Xp11 near the MAO loci found a LOD of 1.97 under a dominant model for DXS7 in a set of 92 sib pairs selected for maternal inheritance. In a second analysis, 34 families not selected for inheritance pattern gave a LOD of 2.16 at MAOB under a dominant model [Dann et al., 1997]. Results from a number of recent genome screens have suggested a possible X chromosome locus, but these results are of weaker magnitude than the most positive loci in these studies [Paterson et al., 1999]. The Cardiff sib pair study produced weak signals in male-male pairs, giving a LOD of 1.45 at DXS993 (p11.4—p11.3) and 1.33 at DXS8092 (q21) [Norton et al., 1999]. DXS993 lies in the same region as DMS1, however, a male specific transmission ratio distortor [Naumova et al., 1998], that makes interpretation difficult. Data from the Oxford/SUNY sample gave a LOD of 1.40 at DXS1068 (p21.1–p11.4) under a very narrow definition, with the most of the LOD coming from 21 female–female pairs, and 1.33 at DXS1227 (q26), with all of the LOD coming from 125 male–male pairs [DeLisi et al., 1998]. Data from the Finnish study found a LOD of 2.01 at MAOB (p11.4–p11.3) [Hovatta et al., 1999]. Results from the X chromosome are summarized in Figure 15.

## DISCUSSION

### What Do the Data Mean?

Numerous authors have suggested that linkage tests for complex traits be interpreted relative to the probability of observing results by chance in a complete screen of the genome [Morton, 1955; Lander and Kruglyak, 1995]. Lander and Kruglyak suggest that nominal *P*-values of 0.000049 (for parametric analysis) or 0.000022 (for nonparametric analysis) will be observed by chance in 5% of genome screens, giving an approximate cut-off for 'significance' in linkage studies. This is equivalent to a LOD of 3.3 or an NPLZ of 3.6, very similar to Morton's original proposal for Mendelian traits. Nominal *P*-values of 0.0017 and 0.00074 will be observed by chance once per genome scan, and they suggest these as cut-offs for 'suggestive' linkage, equivalent to a LOD of 1.9 or an NPLZ of 2.2. No linkage studies of schizophrenia have ever produced 'significant' results under these criteria. Even the original report on chromosome 6p from the ISHDSF, that did achieve this level of significance, would require correction for the numerous models tested.

***The data for schizophrenia are most compatible with several genes all having $\lambda_s$ less than 2.***

This is likely to be due to the small genotype relative risks (GRR) associated with any individual gene contributing to susceptibility to schizophrenia. Calculations show that the numbers of families required to detect linkage depend strongly on both the population frequency of the risk allele, that is likely to be relatively high for schizophrenia susceptibility loci, and GRR [Risch and Merikangas, 1996]. If GRR for a particular genotype is 4 and the allele frequency in the population is between 10 and 50%, then the number of families required is roughly 200–300, a large but just about practical sample size. If, however, the GRR is 2 (and the frequency is in the same range) then the number of families 2500–5400. If the GRR drops to 1.5, the number of families increases to 18,000–68,000, and these numbers are clearly not practical. GRR can be converted into the relative risk measure most widely used currently, $\lambda_s$ [Scott et al., 1997]. If GRR is <2, $\lambda_s$ is <1.3. The data for schizophrenia are most compatible with several genes all having $\lambda_s$ less than 2 [Risch, 1990], and the sample sizes currently held seem to be inadequate to generate unequivocal results.

### Why Have Replications Not Succeeded?

Results are also often of lesser magnitude when new data are added to the sample, as in the collaborative replication study of chromosomes 3, 6 and 8 [Levinson et al., 1996]. The simplest interpretation of these differences is random variation. Simulation studies suggest that in a polygenic disease, initial positive findings may be difficult to replicate, and require much larger samples than the original, because detection of linkage with any one of several susceptibility loci is always more probable than replication of just one specific locus [Suarez et al., 1995].

### Are the Same Genes Involved in Different Populations?

The molecular data are, at present, confusing for a variety of possible reasons. Although it has become the orthodox view that there is no difference in the incidence of schizophrenia across different populations, the main study on which this is based [Sartorius et al., 1986] lacked power to formally test this hypothesis [Frangou and Murray, 1997]. Recent molecular data also cast some doubt on the belief that the genetic inputs to schizophrenia are the same across different ethnic groups. In the NIMH/Millenium genome screen, for example, 5 loci gave suggestive results in the African American families (4q, 6q, 8p, 9q and 15q) and where data exist in the South African Bantu sample (8p, 9q, 15q), these two samples suggest the same loci. A totally different locus, on 10p, gave suggestive results in the NIMH/Millenium European American families. Two further studies of European populations have produced suggestive evidence for this locus, but neither of these samples detected it

originally. Conversely, one of the loci detected in the two African-descended samples was originally detected in the Utah family sample, but has not been detected in other European derived samples. There are almost certainly differences between ethnic groups in the frequency of particular risk alleles (leading to diminished power to detect such loci in one group and increased power in another), but it seems premature to assume that the actual genes involved are significantly different around the world.

### The Putative Loci: What Are We Looking For?

It has become clear over the last ten years that mutations in the coding sequence of genes are not the only way to produce illness. Much of what we currently know about complex trait genetics comes from the study of insulin dependent diabetes mellitus (IDDM). In genome wide studies, affected sib pairs share alleles IBD significantly more often than expected by chance at numerous loci. After the HLA region on chromosome 6 (responsible for the autoimmune destruction of the pancreatic beta cells), the locus with the greatest degree of excess sharing was the insulin gene on chromosome 11 [Davies et al., 1994]. This locus had long shown association with IDDM [Bell et al., 1984] but had been excluded from linkage using parametric analysis [Hitman et al., 1985; Ferns et al., 1986; Elbein et al., 1988; Donald et al., 1989]. Further, the effect at the insulin gene is now known to be a quantitative one. A variable number of tandem repeats (VNTR) polymorphism lies between the promoter and the start of the first exon [Bell et al., 1982], and IDDM susceptibility at this locus is determined by this VNTR [Bennett et al., 1995]. Transcription of the insulin gene (and thus insulin expression) is regulated by alleles of this VNTR [Kennedy et al., 1995], and *all* alleles of this variable DNA region are within the range of normal variation.

***Mutations in the coding sequence of genes are not the only way to produce illness.***

Much has also been written about anticipation and dynamic mutations in schizophrenia. The term anticipation, meaning earlier onset and more severe course in successive generations was first put forward in the context of 'inherited insanity' [Mott, 1910]. Some studies have shown evidence for earlier onset and more severe course measured by age of first, and total frequency of, hospitalization in the schizophrenic offspring of schizophrenics [Bassett and Honer, 1994; Asherson et al., 1994; Chotai et al., 1995; Yaw et al., 1996; Gorwood et al., 1997; Imamura et al., 1998; Heiden et al., 1999] but these results need to be treated cautiously because of a variety of potential biases originally pointed out by Penrose [Asherson et al., 1994].

Two molecular techniques exist for detecting dynamic mutations, the expanding, unstable trinucleotide repeats that cause anticipation [Schalling et al., 1993; Lisitsyn et al., 1994], but are limited by technical difficulty on one hand, and lack of specificity or chromosomal localization on the other. Such studies have shown increased sizes of ligation products in schizophrenics, but there is large overlap between the product sizes in schizophrenics and normals, and the differences are not specific to schizophrenia [Morris et al., 1995; O'Donovan et al., 1996; Bowen et al., 1996; Gaitonde et al., 1997; Speight et al., 1997; Vincent et al., 1998; Burgess et al., 1998; Laurent et al., 1998; Li et al., 1998a; Martorell et al., 1999]. Studies of trinucleotide repeats in known genes have been disappointing. For example, a novel gene hSKCA3, containing a trinucleotide repeat, was mapped to the region of interest on chromosome 22 [Chandy et al., 1998] and showed some association with schizophrenia [Bowen et al., 1998; Stober et al., 1998]. Many studies of this gene followed, predominantly negative [Li et al., 1998b; Wittekindt et al., 1999; Joober et al., 1999; Bonnet-Brilhault et al., 1999], and ultimately this gene was shown to map not to the putative linkage region on 22q, but to chromosome 1 [Dror et al., 1999]. Whether this gene is associated with schizophrenia or not remains unclear, though apparently unlikely.

### The Way Forward?

The possibility of genome wide searches for linkage disequilibrium has been proposed in the past [McGuffin et al., 1992] but this has usually been dismissed as unfeasible. Recent advances encourage greater optimism and Risch and Merikangas suggest that testing every gene in the genome for association may ultimately be more practical than a linkage approach [Risch and Merikangas, 1996]. For example, a locus with GRR of 1.5 would require 950–2200 trios (parents and one affected child) or 500–900 sib pairs for detection compared with a sample size of 18,000–68,000 families required to detect linkage. Not every gene in the genome is yet known or characterized, however, so this approach is not yet practicable. High density, high throughput mapping may be available soon using methods that detect single nucleotide polymorphisms on micro-arrays. Other methods using DNA pooling are already being employed in attempts to screen whole chromosomes for linkage disequilibrium with complex traits [Hill et al., 1999; Fisher et al., 1999]. The most important realization is that even for allelic association studies, the necessary sample sizes are far larger than has previously been thought. Future studies therefore will need, as before, to pragmatically combine candidate gene and

***Testing every gene in the genome for association may ultimately be more practical than a linkage approach.***

systematic searches and strive to maintain diagnostic reliability and comparability, but they will also need to pay proper heed to power.

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